UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,208	09/01/2005	Anita Mehta	RLL-258US	8617

26815 7590 12/21/2006

RANBAXY INC.
600 COLLEGE ROAD EAST
SUITE 2100
PRINCETON, NJ 08540

EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,208	MEHTA ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-8* is/are rejected.

7)☒ Claim(s) *2,3,9 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/11/06; 9/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 are currently pending in the instant application.

Priority

This application is a 371 of PCT/IB02/02984, filed on 07/31/2002. No claim for priority has been made.

Information Disclosure Statement

Applicants' information disclosure statements (IDS), filed on 4/11/2006 and 09/01/2005 have been considered. Please refer to Applicants' copies of the 1449 submitted herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 & 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of the Formula I, including enantiomers, diastereomers, N-oxides and pharmaceutically acceptable salts thereof; the specification is not enabled for *solvates, esters, polymorphs, prodrugs or metabolites* thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'."

In re Wands, 8 USPQ2d 1400 (1988), discusses the following factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph:

1. ***The nature of the invention;***
2. ***The state of the prior art;***
3. ***The predictability or lack thereof in the art;***
4. ***The amount of direction or guidance present;***
5. ***The presence or absence of working examples;***
6. ***The breadth of the claims;***
7. ***The quantity of experimentation needed; and***
8. ***The level of skill in the art***

each of which is discussed in turn below.

The Nature of the Invention

The nature of the invention is the compounds of Formula I, including all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites thereof.

The state of the prior art and the predictability or lack thereof in the art

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the

drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as *polymorphs* and *solvates* are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization, (Morissette *et al.* Advanced Drug Delivery Reviews **2004**, *56*, 275-300).

For instance, the phenomenon of polymorphism, in the crystallization of organic compounds, is of crucial importance to the pharmaceutical industry. Two polymorphs of the same drug molecule may have different physical properties: e.g. solubility, bioavailability, melting points, density, hardness, or color; and may have dramatically different properties that effect the scale-up process. Due to the differences between

polymorphs, the drug regulatory authorities (e.g. the FDA) are increasingly demanding more information about potential drug products before granting approval. The conditions under which polymorphs interconvert is also of crucial importance, particularly when drugs may encounter exposure to changes in temperature, pressure, and relative humidity during processes such as drying, granulation, milling, compression, and storage. Therefore, for these reasons, the state of the prior art is one of unpredictability. The science of crystallization has evolved such that said differences in properties implies patentable distinctiveness between polymorphs.

The state of the prior art is that *prodrugs* are an inactive form of a drug that exerts its effects after metabolic processes within the body convert it to a usable or active form. In other words, a prodrug is a drug that must be activated before it can produce a physiological effect. Prodrugs are designed to be appended to a particular functional group such as a carboxylic acid, alcohol, amine, phosphate, or phosphonic acid. Research is required to match the prodrug with the particular drug to overcome challenges including stability, rate of systemic prodrug cleavage, and safety. Furthermore, it needs to be decided what enzyme system is wanted to cleave the prodrug followed by the evaluation of the prodrug analogs in assays to measure progress in achieving the desired properties (stability, solubility, cleavage of prodrug in biological matrices, pharmacokinetics in animal models, efficacy in animal models, and safety in animal models). This process is exactly like the process used to discover the active drug. The difficulty of discovering effective prodrugs is often underestimated and for all of the aforementioned reasons, the claimed invention is highly unpredictable.

Amount of direction/guidance & presence or absence of working examples

The direction or guidance present in the instant specification for the preparation of the compounds of Formula I is found on pages 6 and 11-23 of the specification. Further, the preparation of suitable pharmaceutical salts of these compounds is discussed on page 8, lines 5-13 in the specification. With respect to prodrugs, page 3 of the specification recites only a definition and the statement, "Conventional procedures for the selection and preparation of suitable prodrugs are known to the artisan skilled in the art."

No direction or guidance is found in the specification for solvates, esters, polymorphs, prodrugs or metabolites of Formula I. In addition, there are no working examples present in the disclosure other than for the compounds of Formula I.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include compounds of Formula I, including all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites thereof.

The quantity of experimentation necessary

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare any *solvates, esters, polymorphs, prodrugs or metabolites* of a compound of Formula I as instantly claimed. The science of crystallization has evolved such that, without guidance or working examples for polymorphs in the specification, the claims lack enablement.

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which prodrug design (functional group manipulation), metabolite, solvate, ester, or polymorph will work for this class of compounds to determine if they would be encompassed in the instant claims, with no assurance of success.

This rejection can be overcome by deleting the unsupported language.

Claims 4-7 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compositions and a method of treatment for urinary and bladder problems, does not reasonably provide enablement for the treatment or prophylaxis of any disease or disorder, mediated through muscarinic receptors, involving the respiratory, urinary and gastrointestinal systems. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The nature of the invention is compounds and compositions of Formula I, the process for preparing these compounds, and methods of using these compounds.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a treatment for urinary and bladder disorders, but not any and all diseases and disorders pertaining to all of the muscarinic receptors. The compounds of Formula I are designed as derivatives of Oxybutynin, a compound marketed for the treatment of urinary and bladder disorders. No other structurally analogous compounds were found.

The amount of direction or guidance present and the presence or absence of working examples

Shown on page 27 of the specification are receptor binding assays comparing the compounds according to Formula I and Oxybutynin. As seen from the data,

Oxybutynin has a M2/M3 selectivity of 7.34, whereas the compounds of Formula I have selectivity ranging from 0.96 to 7.708. Since muscarinic receptors are widely distributed throughout the body, an antimuscarinic action in organs other than the urinary bladder leads to dose-limiting adverse side effects including dry mouth, constipation, blurred vision, headache, somnolence and tachycardia. The selectivity between muscarinic receptors is important for the treatment of diseases claimed, and since there are five distinct muscarinic receptors throughout the body, the selectivity is the crux of the usefulness for these compounds. Therefore, it is not possible for the compounds according to Formula I to treat any or all diseases or disorders mediated through the muscarinic receptors in an efficacious manner.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 4-7 are drawn to "the prophylaxis of a disease or disorder..." Prophylaxis is commonly known to be synonymous with prevention. In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. Deleting the word "prophylaxis" in **Claims 4-7** and an amendment limiting the scope of treatment to what is known in the art may overcome this rejection.

Claim Objections

Claim 2 is objected to because of the following informalities: there should be a comma after each compound name; there should be an ", and" between the last two compound names; and there should be a period at the end of the claim. Appropriate correction is required.

Claims 3, 9 & 10 are objected to as being dependent upon a rejected base, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason M. Nolan, Ph.D.
Examiner
Art Unit 1626

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

Joseph K. M^{c}Kane
Supervisory Patent Examiner
Art Unit 1626
Date: December 18, 2006